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Abstract:	Candidemia is associated with high mortality rate especially in critically ill (ICU) patients with septic shock and echinocandins such as anidulafungin are recommended as first line treatment. Available pharmacokinetic studies of anidulafungin in healthy volunteers and in patients with renal or hepatic impairment showed that no dose adjustment is needed even in patients receiving standard intermittent haemodialysis. However, few data are available with continuous veno-venous haemofiltration (CVVH). In this study the pharmacokinetic of anidulafungin was studied in two ICU patients with candidemia and septic shock undergoing CVVH. Both patients had satisfactory parameters of Cmax (9.04 mg/L and 5.68 mg/L, respectively), AUC (95.18 mg/L*h and 67.48 mg/L*h) and Cmin (2.61 mg/L and 1.43 mg/L). AUC/MIC ratio and Cmax/MIC values were: 11887 and 8435; 1130,25 and 710, for patient 1 and 2 respectively. Our data confirm that in patients with septic shock anidulafungin presents only mild pharmacokinetic changes compared to data reported during CVVH alone.

Introduction

Bloodstream infections caused by *Candida spp*. are associated with a mortality of 30-50%, especially in intensive care units (ICU), where the risk of invasive Candida infection is increased [1]. Echinocandins such as anidulafungin are fungicidal against *Candida spp.* and are recommended as first line agents by the IDSA and ESCMID guidelines[1-3]. Anidulafungin has no known metabolism and undergoes spontaneous degradation at physiologic pH and temperature [4] and pharmacokinetic studies in healthy volunteers and in patients with renal or hepatic impairment demonstrated that no dose change is needed, also including patients undergoing standard intermittent haemodialysis[5-6].

In patients with septic shock the pharmacokinetic of antimicrobials may dramatically change owing to tissue perfusion, change of protein binding, drug clearance and fluid overload which may increase the volume of distribution of many drugs [4]. Continuous veno-venous haemofiltration (CVVH) is frequently used in ICU patients with renal failure and the pharmacokinetic of antifungals may be altered, according to various parameters both patient-related and extracorporeal circuit-related, such as the ultrafiltrate and dialysate rates, dialysate concentrations and the type of membranes.

There are very few data on pharmacokinetic of anidulafungin in ICU patients, either with septic shock or CVVH. The aim of this study was to describe the pharmacokinetics of anidulafungin in two ICU patients with septic shock during CVVH.

Material and methods

Anidulafungin plasmatic concentrations were studied in two ICU patients with septic shock, receiving CVVH and treated with standard dosage (100 mg/die preceded by loading dose of 200 mg, 1 hour of infusion) for candidemia. The area under the curve

(AUC), C_{max} and C_{min} were determined by collecting blood samples during CVVH at 0, 1, 5 and 8 hours after administration at steady state (after the day four from the beginning of maintenance dose). Plasma samples were obtained and centrifuged at 3000 rpm for 10 minutes at 4°C; two samples were stored at -20°C until analysis. Anidulafungin was determined in plasma by ultra performance liquid chromatography-photo diode array detection (UPLC-PDA); a linear forced through zero calibration curve in the range of 15 mg/L to 0.117 mg/L, was used. Mean accuracy expressed as relative accuracy % was 94.4%. Precision, expressed as relative standard deviation %, was 6.39. Pharmacokinetic data were obtained using Kinetica Software (Thermo Scientific, Waltham, Massachusetts, USA). A non-compartmental steady state model was used.

The patients main clinical, microbiological and laboratory data are illustrated in Table 1. Notably, patient 2 was receiving tacrolimus and cyclosporine because of heart transplant.

Results

Patients' clinical and microbiological characteristics are illustrated in Table 1. Mean Cmax, Cmin, AUC, half life, clearance and volume of distribution were: 9.04 Vs. 5.68 mg/L; 2.61 Vs. 1.43 mg/L; 95.18 Vs. 67.48 mg/L*h; 31.99 Vs. 15.34 h; 2.6 Vs. 1.48 L/h; 48.48 Vs. 32.81 L for patient 1 and 2,respectively.

Discussion

The effect of septic shock on serum drug concentrations may be altered owing to increased cardiac output, infusion of liquids, increased or decreased clearances with secondary alterations of the volume of distribution; such changes may result in insufficient dosages of antimicrobials, either for concentration- and time-dependent molecules. Echinocandins are fungicidal against *Candida spp.* and are concentration-dependent with best activity described by C_{max}/MIC and AUC/MIC [4, 6]: anidulafungin

has the highest volume of distribution and, at least in theory, plasma concentration in patients with septic shock may vary even if lipophylic molecules, such as anidulafungin, better tolerate changes in body fluid volume [7, 8]. In ICU patients CVVH is commonly used in septic patients with renal failure and it may further contribute to pharmacokinetic alterations, depending on several variables, such as the ultrafiltrate and dialysate rates and the type of membrane used.

Available data in non-ICU population pharmacokinetic analysis for anidulafungin show that pharmacokinetic parameters associated with success include AUC at steady state >35 mg/L*h and minimum plasma concentration at steady state (C_{min}) >1 mg/L[6]. The strongest relationship with antifungal effect in animal models, considering the pharmacokinetic/ pharmacodynamic parameters, was observed with AUC/MIC ratio of 250 and C_{max}/MIC > 4 [5, 9].

Our patients did achieve AUC/MIC >250 and C_{max}/MIC > 4, perhaps due also to the very low MIC of *C. albicans* tested. These results underscore that even in patients with septic shock receving CVVH anidulafungin has a very good pharmacokinetic profile. According to the available literature, both patients (1 and 2, respectively) had satisfactory parameters of C_{max}, AUC and C_{min}. AUC/MIC ratio and C_{max}/MIC values considering the MIC for *Candida albicans* (0.008 mg/L) were 11887 and 8435; 1130,25 and 710, respectively, for patient 1 and 2. Notably, pharmacokinetic data for patient 2 confirm that there are no significant interactions with tacrolimus or cyclosporine.

Of course we proceeded to simulate AUC/MIC ratio for different Candida MICs: the ratios were 5948 and 4217 for patient 1 and 2, respectively, with MIC of 0.016 mg/L; 761 and 539 for MIC of 0.125 mg/L. The simulated values of C_{max}/MIC considering MIC values of 0.016 mg/L were 565.13 and 355, changing to 72.34 and 45.44 for patient 1 and 2, respectively with MIC of 0.125 mg/L. Despite early and appropriate empiric treatment

with anidulafungin before microbiological confirmation of candidemia and plenty satisfaction of pharmacokinetic parameters, both patients were dead at 21 days after diagnosis, with negative blood cultures at 48 hours after diagnosis.

To our knowledge there are few data on pharmacokinetic of anidulafungin in ICU patients and no data are available in patients with septic shock undergoing CVVH. A case report in the ICU setting by Burkhardt reported that anidulafungin does not necessitate dose adjustment with septic shock undergoing extended daily dialysis [10]. However, pharmacokinetic parameters were only studied at the first day of treatment, when the loading dose was administered: C_{max}, C_{min} and AUC values were 5.32 mg/L, 1.60 mg/L and 55.2 mg *h/L, respectively. Leitner et al. described 10 patients receiving CVVH, three of which with septic shock, with a CVVH ultrafiltration rate of 1500 ml/h, an extended 3-h anidulafungin loading dose infusion and 1.5-h infusion mainteinance dose [11]. C_{max} values were evaluated at day 1, 2 and 3 whilst AUC was determined only during the first day. This study reported a mean C_{max} of 5.9+ 2 mg/L at day 3 and a mean arterial AUC of 109.9+ 49.82 mg*h/L at day 1. According to these data, the Authors concluded that dose changes are not needed during CVVH.

In conclusion, anidulafungin treatment of ICU patients with septic shock and CVVH did confirm that no dose changes are needed compared to patients treated with CVVH alone.

Table 1. Patients' clinical and microbiological characteristics.

	Patient 1	**Patient 2**
Sex	Female	Male
Age (year)	69	56
BMI	28	31
Comorbidities	Hypertension, diabetes, ischemic cardiopathy. Berger's nephritis. Peritoneal dialysis. Prosthetic aortic valve	Diabetes. Heart transplant complicated by surgical site infection and AKI. Immunesuppression with tacrolimus and cyclosporine
Days of ICU at diagnosis	20	24
Creatinine (mg/dl)	2.3	2.2
Albumin (mg/dl)	2.4	2.5
AKI/CRF	CRF	AKI
Therapy with Amine yes/no	Yes	Yes
Blood cultures	*C. albicans*	*C. albicans*
CVVH (ml/h)	2000	1800
MIC for Anidulafungin (mg/L)	<0.008	<0.008
Candida score[12]	4	4

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